KEY PAPER EVALUATION

Canagliflozin – something new for type 2 diabetes, but is it safe and efficacious?

Evaluation of Inagaki N, Kondo K, Yoshinari T et al. Efficacy and safety of canagliflozin in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, 12-week study. Diabetes Obes Metab 2013; doi: 10.111/dom.12149 [Epub ahead of print] and Cefalu WT, Leiter LA, Yoon KH et al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomized, double-blind, phase 3 non-inferiority trial. Lancet 2013;382:941-50

Abstract

***Introduction*:** Inhibition of the sodium-glucose cotransporter 2 (SGLT2), to promote the excretion of glucose, is a new paradigm in the treatment of type 2 diabetes.

Areas covered: Canagliflozin is a SGLT2 inhibitor, which has been the subject of two recent clinical trials, which are evaluated.

***Expert Opinion*:** Studies with canagliflozin, in subjects with type 2 diabetes, have shown its use is associated with reductions in HbA1c and body weight, small reductions in blood pressure and triglycerides, while increasing HDL cholesterol and LDL cholesterol. As monotherapy in Japanese subjects, or in comparison with glimepiride in CANTATA-SU (CANagliflozin Treatment And Trial Analysis versus SUlphonylurea), canagliflozin causes a low incidence of hypoglycemia, and this is an advantage over glimepiride. However, one of the disadvantages with canagliflozin, which was also highlighted in CANTATA-SU, is that canagliflozin can cause urogenital infections, which are not observed with other anti-diabetic drugs. The Federal Drug Administration (FDA) has recently approved canagliflozin for use in type 2 diabetes, while directing that a clinical outcome safety trial be undertaken. We are concerned that canagliflozin has been approved for use in type 2 diabetes prior to a clinical outcome study of efficacy being undertaken, and without the outcome of further safety testing.

Key words: canagliflozin, CANTATA-SU, clinical trials, HbA1c, type 2 diabetes

1. Introduction

In the United States, the prevalence of diabetes is about 8% (24 million people), and 90% of this is diabetes type 2, which has both lifestyle and genetic components [1]. Despite the treatments available for type 2 diabetes, about two thirds of the subjects die from heart disease or stroke. Diabetes is also a leading cause of blindness, end-stage kidney failure, and lower limb amputations [1]. Clearly, there is a need for good treatments for type 2 diabetes.

In subjects with type 2 diabetes, when lifestyle changes have failed to manage the diabetes, medications are used. Metformin is the medication of first choice in subjects with type 2 diabetes. When lifestyle changes and the highest tolerated dose of metformin fail to control the diabetes, a sulfonylurea is often added. The thiazolidinediones are an option as dual or additional therapy with metformin and/or a sulfonylurea. The revelation that insulin secretion is under the control of a gut hormone, glucagon-like peptide 1 (GLP-1) led to a new paradigm in the management of type 2 diabetes; medicines that directly stimulate e.g. exenatide, or that prolong the actions of the endogenous GLP-1 at its receptors i.e. the gliptins. Finally, when oral medications do not control type 2 diabetes, injectable insulin is added. Despite these medicines, type 2 diabetes is often progressive, with subjects unable to maintain long-term glycaemic control [2]. Also, some of these diabetic medicines (notably insulin and the sulfonylureas) increase body weight, which contributes to the diabetes.

Some recent physiological discoveries have opened up a new paradigm in the treatment of diabetes. The sodium-glucose cotransporters (SGLTs) control the transport of glucose across the intestinal epithelium and proximal kidney tubules (reviewed in [3]). SGLT2 in the kidney accounts for 90% of the reabsorption of glucose [3]. Inhibition of SGLT2 leads to glucosuria, and may be beneficial in the treatment of type 2 diabetes [3]. One of these SGLT2 inhibitors is canagliflozin, and this evaluation is of two recently published trials with this compound as monotherapy. The first is a placebo-controlled trial of canagliflozin as monotherapy in Japanese subjects with type 2 diabetes. The other trial is a comparison of canagliflozin with the sulphonylurea glimepiride in subjects with type 2 diabetes inadequately controlled with metformin: CANTATA-SU (CANagliflozin Treatment And Trial Analysis versus SUlphonylurea); section 3. Both trials show the short-term ability of canagliflozin monotherapy to reduce HbA1c.

2. Placebo-controlled trials with canagliflozin monotherapy in Japanese subjects

2.1 Background

Prior to the Japanese study, a randomized, double-blind, placebo-controlled Phase 3 trial of canagliflozin monotherapy, was undertaken in 17 countries over a 26 week period, which enrolled 584 subjects with type 2 diabetes [4]. Baseline HbA1c was 8.0%, and this increased by 0.14% in the placebo group, while being reduced by 0.77% and 1.03% with canagliflozin 100 and 300 mg, respectively [4]. The participants in the 100 mg and 300 mg canagliflozin groups had a higher incidence of genital mycotic infections (2.5% and 5.6% for males; 8.8% and 7.4% for females, respectively), than in the placebo group (males 0% vs. females 3.8%) [4]. There was a low and similar incidence of hypoglycemia in the placebo and canagliflozin groups [4]. Recently, a study was undertaken to determine whether the findings with canagliflozin monotherapy in Japanese subjects were similar to those reported in this international study.

2.2 Placebo-controlled trial in Japanese subjects

The methods and results of the Japanese study demonstrating that canagliflozin is more effective than placebo at improving glycaemic control and weight loss in Japanese subjects with type 2 diabetes [5] are summarized within this section. To be included, subjects were required to: have an HbA1c of 6.9-9.9%; be aged between 20 and 80 years; have had type 2 diabetes for no less than 3 months prior to the run-in period; and have participated in diet and exercise regimes with no alterations to this for ≥ 8 weeks prior to the commencement of the study. Subjects were excluded if they previously or currently had any serious diabetic complications (such as diabetic ketoacidosis, proliferative diabetic retinopathy, serious diabetic neuropathy, stage 3 or overt diabetic nephropathy), renal glycosuria, a Fasting Plasma Glucose (FPG) ≥270mg/dl and hereditary glucose-galactose malabsorption or were recommended for insulin therapy.

Subjects with type 2 diabetes were required to undergo a washout period prior to starting treatment if they were previously being treated with any anti-hyperglycemic agents. The 382 enrolled subjects had an average HbA1c level of 8.09%, and a mean age of 57 years. Participants were randomized to either canagliflozin 50 mg, 100 mg, 200 mg, 300 mg or a placebo group.

The primary endpoint was the change in HbA1c levels from baseline to week 12, with average reductions of 0.61%, 0.80%, 0.79% and 0.88% for canagliflozin 50, 100, 200 and 300 mg, compared to a 0.11% increase in the placebo group, respectively. All doses of canagliflozin were superior to the placebo, and the higher doses of canagliflozin (100, 200, 300 mg) were superior to the lower (50 mg) dose. One of the secondary endpoints was FPG, which was reduced by 3.0, 24.7, 33.1, 36.1, 38.3 mg/dl with the placebo, 50, 100, 200, 300mg canagliflozin respectively.

Canagliflozin resulted in changes in the urinary glucose/urinary creatinine ratio, with Urinary Glucose Excretion increasing significantly (33.9, 45.1, 55.5 and 60.6 g glucose/g creatinine) with 50, 100, 200 and 300 mg of canagliflozin respectively compared to the placebo (0.03 g glucose/g creatinine). Canagliflozin 50, 100, 200, and 300 mg also significantly decreased body weight by 1.98, 2.51, 2.39, and 3.19 kg, respectively, compared to the placebo group (0.75kg).

High-density lipoprotein-cholesterol increased by 0.01, 0.06, 0.12, 0.14, and 0.12 mmol/l, LDL-C measures changed by -0.02, 0.12, 0.13, 0.21, and 0.14 mmol/l, and triglyceride levels reduced by 0.01, 0.12, 0.19, 0.19, and 0.16 mmol/l in the placebo and canagliflozin 50, 100, 200, and 300 mg groups, respectively. Mean systolic blood pressure was reduced by approximately 1.2, 5.8, 7.1, 9.3 and 8.7 mmHg and diastolic blood pressure reduced by approximately 0.9, 2.2, 3.9, 5.1 and 4.2 mmHg for the placebo, canagliflozin 50, 100, 200, and 300 mg groups, respectively.

Hypoglycaemic occurred in 4.9%, 4.1%, 6.5%, and 4% of subjects with canagliflozin 50, 100, 200, and 300 mg, respectively, compared to no reports with the placebo. Two patients being treated with canagliflozin reported a vulvovaginal candida infection – one from each of the 100 and 300 mg groups. There were no reports of urinary tract infections.

3. Canagliflozin vs glimepiride

3.1 Method and results

The methods and results of CANTATU-SU, an international Phase 3 non-inferiority 52-week clinical trial, comparing canagliflozin to glimepiride in subjects with type 2 diabetes [6], are summarized in this section. To be enrolled, subjects had to have an HbA1c of 7.0-9.5%, and were stabilized on a dose of metformin (≥ 2000 mg/day or ≥ 1500 mg/day, if they could not tolerate a higher dose). Subjects were excluded if they had experienced a recent severe hypoglycaemic episode, or impaired kidney or liver function.

The 1450 enrolled subjects had had type 2 diabetes for a mean of 6.6 years, had an HbA1c of 7.8%, and were 56 years old. They were randomized to canagliflozin 100 mg or 300 mg or glimepiride, which was titrated from a starting dose of 1 mg to maximum dose of 6 or 8 mg (as permitted by the country of investigation), and the mean maximum dose was 5.6 mg.

The primary endpoint was the change in HbA1c from baseline to week 52, and this was reduced by 0.82% and 0.93% with canagliflozin 100 and 300 mg, and 0.81% with glimepiride, respectively. Both doses of canagliflozin were non-inferior to glimepiride, and the higher dose of canagliflozin (300 mg) was superior to glimepiride.

Secondary endpoints included fasting blood glucose levels, which were lower with both doses of canagliflozin than with glimepiride. Canagliflozin 100 mg and 300 mg caused small increases in LDL (0.12 and 0.24 mmol/l) and HDL cholesterol (0.08 and 0.10 mmol/l), and decreased triglycerides (0.22 and 0.10 mmol/l, respectively), whereas glimepiride had little or no effect on these.

Canagliflozin at 100 and 300 mg reduced mean systolic blood pressure by 3.5 and 4.6 mmHg and diastolic blood pressure by 1.8 and 2.5 mmHg, respectively, whereas glimepiride had no effect on blood pressure. Canagliflozin at 100 and 300 mg also reduced body weight by 3.7 and 4.0 kg, respectively, whereas subjects taking glimepiride had a small weight gain (0.7 kg). Body composition was assessed for a subset of 198 subjects, which showed the weight loss with canagliflozin was about two-thirds from fat mass and one-third from lean body mass.

The frequency of severe hypoglycaemic (requiring assistance of another individual or resulting in seizure or loss of consciousness) was lower with canagliflozin (<1%) than with glimepiride (3%). The frequency of documented hypoglycaemia (glucose ≤ 3.9 mmol/L with or without symptoms) was also lower with canagliflozin (5-6%) than with glimepiride (34%).

Canagliflozin, 300 and 600 mg caused a higher incidence of genital mycotic infections (7 and 8% in men, 11 and 14% in women, respectively) than with glimepiride (1% in men and 2% in women), and of urinary tract infections (6% vs. 5%). Pollakuria (increased urinary frequency) was also more common with canagliflozin (3%) than with glimepiride (< 1%).

3.2 Discussion

The authors consider that they have titrated glimepiride up to the maximum that can be used without excessive rates of hypoglycaemia, and at this dose (5.6 mg), it has less of an effect on HbA1c than does the higher dose of canagliflozin [6]. The authors also point out that the weight loss with canagliflozin is an advantage over some of the other anti-diabetes medicines (sulphonylureas, insulin, and thiazolidediones) which cause an increase in body weight [6].

4. Expert Opinion

4.1 Body composition study

In CANTATA-SU, body composition was assessed for a subset of 198 subjects, and from this subset it was claimed that canagliflozin predominantly caused weight loss from fat mass [6]. However, it is not explained how this subset were selected, and whether they matched the total population in CANTATA-SU. For instance, the population in CANTATA-SU is predominantly White (67%), Asian (20%), or Black/African American (4%) [6]. However, we do not know anything about the subset.

Thus, to clarify, the demographics of the subset should be given, and compared to the total population.

4.2 Effect on lipids

Canagliflozin causes small increases in LDL cholesterol and HDL cholesterol, but decreases triglycerides [4, 5, 6]. These changes have been largely dismissed by the authors, as they are small [4, 5, 6]. However, it should be noted, that when rosiglitazone, a thiazolidinedione used in the treatment for diabetes, was being developed, it too was shown to cause small increases in LDL cholesterol and HDL cholesterol, but decrease triglycerides, and these changes were considered to be small and not likely to be clinically significant [7]. Subsequently, rosiglitazone was shown to have no benefit or to increase cardiovascular risk, and it has been suggested that these changes in lipids may contribute to the lack of cardiovascular benefit with rosiglitazone [8]. Thus, it is important to determine the mechanism of canagliflozin which leads to these effects on lipids, and whether it contributes to the long term cardiovascular effects of canagliflozin. Unlike rosiglitazone, canagliflozin causes weight loss which may contribute to the beneficial effects on HDL cholesterol and triglycerides. However, the mechanism underlying the small increase in LDL cholesterol is unknown.

4.3 Exclusion of subjects with kidney impairment

In CANTATA-SU, subjects with kidney impairment (glomerular filtration rate of < 55 mL/min/1.73 m^2 or < 60 mL/min/1.73 m^2 if based on restriction of metformin use in local label) were excluded from treatment with canagliflozin [6]. In another study, in subjects with type 2 diabetes and stage 3 chronic kidney disease, it was shown that canagliflozin 300 mg for 16 weeks was effective in promoting glucose excretion and reducing HbA1c in subjects with a glomerular filtration rate of ≥ 30 and < 50 ml/min/1.73 m^2 [9]. In these subjects, canagliflozin use was associated with a short-term reduction in glomerular filtration rate, and an increase in blood urea nitrogen, which are potentially detrimental effects [9]. Canagliflozin also decreased the urine albumin/creatinine ratio, and slowed the progression of normo-albuminuria to micro- or macro-albuminuria, which indicate potential beneficial effects on the kidney [9]. Longer studies are needed to test the efficacy and safety of canagliflozin in subjects with kidney disease. This is an important area of study, as subjects with diabetes often develop chronic kidney disease, and the use of the antidiabetic medicines (metformin and the thiazolidinediones) is restricted in kidney disease.

4.4 Urogenital infections with canagliflozin

An increased incidence of urogenital infections is associated with canagliflozin, and is responsible for discontinuation in a small number of subjects. Thus, the international canagliflozin monotherapy study found the incidence of genital mycotic infections to be 8.8% and 7.4% in females, and 2.5% and 5.6% in males, and urinary tract infections, 7.2% and 5.1% with canagliflozin 100 and 300 mg, respectively [4]. The Japanese canagliflozin monotherapy study reported two vulvovaginal infections with canagliflozin (Section 2). The CANTATU-SU study found 300 and 600 mg of canagliflozin caused a high incidence of genital mycotic infections and urinary tract infections compared with glimepiride (Section 3). Other trials have also reported an increased incidence of urogenital infections with canagliflozin [9,10,11].

Dapagliflozin, like canagliflozin, is a sodium-glucose cotransporter 2 inhibitor for treatment of type 2 diabetes [12]. Dapagliflozin has also been shown to cause urogenital infections [12]. This suggests that urogenital infections, with a higher incidence in females than males, are an adverse effect associated with SGLT2 inhibitors. It is important that health professionals are made aware of this potential adverse effect with SGLT2 inhibitors.

4.5 Hypoglycemia

Both canagliflozin monotherapy studies [4, 5] and the comparison of canagliflozin with glimepiride [6] demonstrate the low incidence of hypoglycemia with canagliflozin. The FDA voted 10 to 5 in favor of approving canagliflozin, and gave the absence of hypoglycemia as one of the deciding factors [13]. In CANTATU-SU, which showed less hypoglycemia with canagliflozin than glimepiride, subjects who had had a recent severe hypoglycemic episode were excluded [6]. Thus, a further study to test canagliflozin in subjects with type 2 diabetes, who have a history of hypoglycemia episodes, should be undertaken to determine whether canagliflozin is a useful alternative medicine in these subjects.

4.6 Clinical outcomes studies

When approving canagliflozin (Invokana) in March, 2013, the FDA required five postmarketing studies, which included a pharmacovigilance program, a bone safety study, two pediatric studies, and a cardiovascular safety outcomes trial [14].

In our opinion, one of the major limitations to the studies to date with canagliflozin is that no clinically beneficial outcomes (e.g. on cardiovascular mortality and morbidity) have been published in the peer reviewed literature for this medicine. CANVAS (CANagliflozin cardiovascular Assessment Study) was initially set up to have a first phase to establish the safety and tolerability of canagliflozin, and then more subjects would be part of the second phase to give a total of 18000, which would be

a cardiovascular outcomes study with a primary outcome of the composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke [15]. However, after the first phase, CANVAS was unblinded to produce the safety and tolerability data for the regulatory bodies [15]. The data from CANVAS submitted to the FDA did not show an increased risk of cardiovascular risk with canagliflozin [16]. However, there was a 46% increased risk of stroke, particularly within the first 30 days of treatment with canagliflozin, although the numbers were small [16].

The second phase of CANVAS is not proceeding i.e. the outcomes study [15]. Instead, the first phase of CANVAS of 4330 subjects with type 2 diabetes is ongoing as a cardiovascular safety study [15]. However, the modified CANVAS has reduced numbers and power than the originally planned second phase, and a planned finish for 2015 [15]. As CANVAS is now a safety and smaller study, it is not likely to be able to determine whether canagliflozin has beneficial effects on cardiovascular outcomes.

We would have preferred that the FDA postpone considering canagliflozin for approval until cardiovascular outcome trials were completed, with both efficacy and safety outcomes. The precedent for this is that other anti-diabetes medicines have been approved by the FDA, and subsequently shown to have no benefit or increase cardiovascular risk. These include rosiglitazone, which is discussed in section 4.2, or more recently, the gliptins; alogliptin [17] and saxagliptin [18], which do not alter cardiovascular risk, compared to placebo. Thus, it is not clear to us, why some of these drugs are still available for clinical use, and why further drugs would be approved without showing cardiovascular benefit.

4.7 Canagliflozin – something new for type 2 diabetes, but is it safe and efficacious?

Clinical trials have shown that canagliflozin use is associated with a reduction in HbA1c, body weight, blood pressure, triglycerides, while increasing HDL cholesterol and LDL cholesterol. Although canagliflozin may have advantages over other anti-diabetic drugs, as it causes a low incidence of hypoglycemia, this is countered by the disadvantage of causing urogenital infections, which are not observed with other anti-diabetic drugs. We are concerned that the FDA has approved canagliflozin for use in type 2 diabetes prior to the completion of a clinical outcome study of efficacy, and further safety testing. We suggest that canagliflozin should not be widely used in subjects with type 2 diabetes until such studies have been completed.

References

1. Ligaray KPL, Isley WL. Diabetes mellitus, type 2. http://emedicine.medscape.com/article/117853-overview (Accessed 24/9/2013)
2. Koro CE, Bowlin SJ, Bourgeois N, Fedder DO. Glycemic control from 1988 to 2000 among U.S. adults diagnosed with type 2 diabetes: a preliminary report. Diabetes Care 2004;27:17-20.
3. Bakris GL, Fonseca VA, Sharma K, Wright EM. Renal sodium-glucose transport: role in diabetes mellitus and potential clinical implications. Kidney Int 2009;75:1272-77.
4. Stenlof K, Cefalu WT, Kim KA, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes Obes Metab 2013;15(4):372-82.
5. Inagaki N, Kondo K, Yoshinari T, et al. Efficacy and safety of canagliflozin in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, 12-week study. Diabetes Obes Metab 2013; doi: 10.111/dom.12149 [Epub ahead of print]
6. Cefalu WT, Leiter LA, Yoon KH, et al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomized, double-blind, phase 3 non-inferiority trial. Lancet 2013;382:941-50.
7. Doggrell SA. Clinical trials with thiazolidinediones in subjects with Type 2 diabetes – is pioglitazone any different from rosiglitazone. Expert Opin Pharmacother 2008;9:405-20.
8. Consoli A, Gormoso G. Do thiazolidinediones still have a role in treatment of type 2 diabetes mellitus. Diabetes Obes Metab 2013;15:967-77.
9. Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. Diabetes Obes Metab 2013;15:463-73.
10. Rosenstock J, Aggarawal N, Polidori D et al. Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. Diabetes Care 2012;35:1232-8.
11. Lavalle-González FJ. Januszewicz A, Davidson J et al. Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomized trial. Diabetologia 2013;56:2582-92.
12. Johnsson KM, Ptaszynska A, Schmitz B, et al. Urinary tract infections in patients with diabetes treated with dapagliflozin. J Diabetes Complications 2013: S1059-8727.
13. FDA approves new diabetes drug, canagliflozin, despite CV concerns. http://theheart.org/article/1523789 (Accessed 15/10/2013).
14. FDA news release: FDA approves Invokana to treat type 2 diabetes http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm345848.htm (Accessed 8/10/2013)
15. Neal B, Perkovic V, de Zeeuw D, et al. Rationale, design, and baseline characteristics of the Canagliflozin Cardiovascular Assessment Study (CANVAS) – A randomized placebo-controlled trial. Am Heart J 2013;166:217-23.
16. Experts express mixed thoughts on canagliflozin approval. Medscape. Apr 18, 2013 http://www.medscape.com/viewarticle/782712_print (Accessed 14/11/2013)
17. White WB, Cannon CP, Heller SR et al. Alogliptin after acute coronary syndromes in patients with type 2 diabetes. N Engl J Med 2013;369:1327-35.
18. Scirica BM, Bhatt DL, Braunwald E et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013;369:1317-26.